REMARKS

Claims 1 - 18 are pending the application; Claims 6-10, 13, 14 and 16 are withdrawn from consideration as drawn to non-elected species; Claims 1 -5, 11, 12, 15, 17 and 18 stand rejected. By this Amendment Claims 6-10, 13, 14 and 16 have been cancelled, Claims 1, 11, 12 and 15 have been amended and new Claims 19-21 have been added. These amendments and new claims add no new matter to the application.

Claims 1-5, 11, 12, 15, 17 and 18 stand rejected under 35 USC 112 as allegedly not enabled; Applicant respectfully traverses these rejections. The Examiner says that each claim is directed to methods of treating beta-amyloid fibril formation, and this is correct. The Examiner further asserts however that the specification does not describe how to practice the claimed methods. This is not true. The claimed methods are simple, and their implementation is well within the grasp of persons having ordinary skill in the art. The Examiner seems most concerned with the reasonable predictability (at the time of invention) of *in vivo* success based on demonstrated *in vitro* results. The Examiner asserts that *in vivo* success could not then have been predicted based on demonstrated *in vitro* results.

Applicant respectfully submits however that Applicant did in fact reasonably so predict *in vivo* success based on demonstrated *in vitro* results, and these predictions have since been borne out, both in further laboratory testing of animals and in subsequent studies by colleagues (see further discussion below).

Applicant asserts that the law does not require that the art already have established such a direct correlation, merely that, as the Examiner herself says, "one has the ability to make and use [the invention] with a reasonable expectation of success. [underline added]" In this case, it turns out it was entirely and imminently reasonable to predict that the demonstrated *in vitro* results would predict the success of *in vivo* results, because that is just what happened.

At the time the application was filed, a working rodent *in vivo* model was already in place, and *in vivo* rodent studies were then planned to confirm the prediction that inhibiting or reversing *in vitro* formation of amyloid proteins and/or peptides would be predictive of *in vivo* performance. Experiments were subsequently completed that in fact did so confirm this *in vivo* performance.

For example, in one experiment, Groups (n=7 per group) of C57/Blk mice were stereotaxically infused for 1 week into hippocampus for 1 week with Aβ 1-40 only, Aβ 1-40 + laminin (or laminin fragments), laminin (or laminin fragments) only in phosphate-buffered saline (PBS). Infusion was achieved by stereotaxically placing a cannula (27 gauge) into hippocampus of each mouse at coordinates of AP ±1.8, ML 1.0, and DV ±2.0. Alzet mini-osmotic pumps filled with infusate were attached to the cannulae to deliver approximately 100 μl of volume over a 1 week period. Infusates were prepared from stock solutions at time of surgery and loaded into preprimed pumps and tubing.

After 1 week of infusion the mice were sacrificed and perfused transcardially, first with a saline flush and followed by paraformaldehyde fixation. Post fixation for 24 hours was performed followed by sucrose infiltration cryoprotection (30% sucrose in SPBS) overnight. Brains were sectioned through the infusion site at 25 μm per section. Standard staining and immunostaining was performed on sections spaced throughout the infusion site. Congo red staining (a marker for fibrillar amyloid) was quantitated by blind scoring on an arbitrary scale of 0 to 5 (with 0 = no amyloid in any site; and 5 = amyloid in areas at and far away from the infusion site).

Groups of mice infused with Aβ 1-40 only had a mean Congo red score of 2.00 +/- 0.53, whereas Aβ 1-40 + laminin (or laminin fragments) had a mean Congo red score of 0.44 +/- 0.18 ($p<0.05$). Therefore in this *in vivo* study, infusion with laminin or laminin fragments was demonstrated to inhibit/reduce fibrillar Aβ amyloid deposits in brain by a highly significant 78%,

thus confirming Applicant's reasonable prediction that the early *in vitro* studies described herein would be quite predictive of subsequent *in vivo* results.

In addition, a number of colleagues have also subsequently confirmed what Applicants had at the time reasonably predicted. For example, several published studies confirm that laminin inhibits Alzheimer's amyloid fibrillogenesis.

1) Morgan and Inestrosa, Braz. J. Med. Biol. Res. 34:597-601, 2001, a review article demonstrating that laminin inhibits Aβ polymerization into fibrils, and is able to protect cells from Aβ neurotoxicity.

2) Morgan et al, Peptides 23:1229-1240, 2003, a study that shows that laminin 1 and laminin 2 induce disaggregation of preformed Aβ fibrils in vitro (Laminin 1 is similar to the laminin fragment disclosed in the specification of this patent application).

Applicant respectfully traverses the Examiner's characterization of the claims as, "the demonstration that laminin or fragments thereof are capable to inhibit amyloid protein formation *in vitro*." In contrast, Applicant submits that their invention is what is so far claimed, and that this includes *in vivo* effectiveness. Applicant also traverses that the references cited by the Examiner (p4 of the Office Action) in any way anticipate or render obvious any of the claims (Applicants note with appreciation that these two references are not cited as prior art against any of the claims). Therefore, it is NOT the state of the art, as of the priority date of this application, that laminin can inhibit amyloid fibril formation *in vitro*, for that is what Applicants themselves have discovered and claimed herein. It is also NOT the state of the art that *in vitro* inhibition is not predictive of effectiveness *in vivo*; rather, what is so is that the art expresses no opinion about whether *in vitro* inhibition is predictive of effectiveness *in vivo*. Thus the art is in fact receptive to the discoveries and disclosures contained in the application as filed.

Applicants express no present opinion on whether there existed as of the filing date any information that would suggest to one skilled in the art that the *in vitro* performance disclosed in the application would be predictive of similar effects *in vivo*; however, the application itself does expressly contain that prediction, and that prediction has since been validated as reasonable. Thus Applicant submits that it is immaterial whether there was an absence of any other such information in the prior art, and that one skilled in the art need only relate to the instant disclosure to practice the claimed invention with success. Such practice would NOT require any knowledge of route, duration or quantity in advance of reading the specification because, Applicant submits, all that information is readily available to one skilled in the art upon appreciation of the specification. It is not merely the disclosed doses and regimes set forth at pages 63-65 of the application that enable the claims for those skilled in the art (a skill level it is submitted that may in some cases exceed the skill level of 'routine practitioners', as opined by the Examiner); it is the application in its entirety that is so enabling. Working examples are provided, and no undue experimentation would be required to administer a therapeutically effective dose of the disclosed proteins to either animal or human, as is evidenced in part by the relative simplicity of the subsequent animal experiment set forth above. Those skilled in the art routinely set and adjust therapeutic dosages for maximum efficacy.

This application is therefore NOT analogous to the cited case, *In re Colianni*, a case believed to be limited to its facts, namely application of ultrasonic energy for fusing bones. In contrast, the instant specification contains a wealth of information for the skilled scientist that were apparently not provide by Colianni. The instant claims and specification are not fairly characterized, as the Examiner calls it, "an invitation to experiment."

Claims 1-5, 11, 12, 15, 17 and 18 are therefore believed to be in condition for allowance and not subject to rejection under section 112; and reconsideration is requested.

Claims 1 and 15 stand rejected under 35 USC 112 as allegedly indefinite; Applicant respectfully traverses these rejections. The Examiner says that each claim has omitted an essential step; the Examiner alleges that each claim fails to include the step that "leads to" the claimed treatment. Applicant respectfully submits that all essential steps are present in the rejected claims. Each claim recites all the essential steps for the claimed treatment, namely, "administering to the patient a therapeutically effective amount of a [selected] polypeptide". Applicant submits that this step alone is sufficient to effect the claimed treatment of inhibiting or reducing beta-amyloid protein formation, deposition or accumulation, all as is well supported in the specification. Claims 1 and 15 are therefore believed to be in condition for allowance, and reconsideration is requested.

The Examiner asserts that "conformation similarity" is vague and ambiguous as used in claims 1-4. Applicant respectfully submits that "conformation" and "conformation similarity" are well defined in the specification (at page 53 for instance):

> "refers to a polypeptide's ability to assume a given shape, through folding and the like, so that the shape, or conformation, of the molecule becomes an essential part of it's functionality, sometimes to the exclusion of its chemical makeup. It is generally known that in biological processes two conformational similar molecules may be interchangeable in the process, even the chemically different. 'Conformational similarity' refers to the latter interchangeability or substitutability. For example, laminin and laminin-derived protein fragments are among the subjects of the invention because they have been shown to bind the Aß protein and render it inactive in fibril formation; it is contemplated that other molecules that are conformationally similar to laminin, or any claimed laminin fragment or polypeptide, may be substituted in the claimed method to similarly render the Aß inactive in fibrillogenesis and other amyloid processes. In general it is contemplated that levels of conformational similarity at or above 70% are sufficient to assume homologous functionality in the claimed processes, though reduced levels of conformational similarity may be made to serve as well. Conformational similar levels at or above 90% should provide some level of additional homologue functionality."

Thus the term is not vague and ambiguous. What is claimed is any compound with the requisite "conformational similarity" to a given fragment of laminin protein. As for the 70% and 90%

limitations, Applicant submits that persons skilled in the art would also have no difficulty with a determination as to whether any protein has 70 - 90 per cent conformational similarity to some other protein. Claims 1-4 are therefore believed to be in condition for allowance and reconsideration is requested.

The Examiner asserts that "therapeutically effective amount" is vague and indefinite as used in claims 1, 15, 17 and 18. Applicant respectfully submits that the term "therapeutically effective amount" is very well known in the art. The therapeutic effect desired is recited in the respective claims, and the precise amount is within the skill of those in the art to determine, and all without any undue experimentation. Claims 1, 15, 17 and 18 are therefore believed to be in condition for allowance and reconsideration is requested.

Claim 11 has been amended to clarify that a preferred laminin fragment includes at least one globular domain repeat within the laminin A chain, thereby providing antecedent for the phrase "globular domain repeats" in amended claim 12, also thus clarified. Claims 11 and 12 are therefore believed to be in condition for allowance, and reconsideration is requested.

New claims 19-21 are believed to be allowable as well, for reasons set forth above, and it is submitted that the new claims do nor require further searching. Claim 19 presents an alternate embodiment of the invention directed to causing the previously claimed effect in "an environment". It is believed that this alternate embodiment is well supported throughout the specification in general, and that such environments include both *in vitro* and *in vivo* environments. Entry of and favorable action on the new claims is therefore requested.

Applicant believes that it has responded fully to all of the concerns expressed by the Examiner in the Office Action, and respectfully requests that the new claims be entered and examined, and that early favorable action be taken on all claims pending in the application. Applicant respectfully requests reexamination of all rejected claims and early favorable action on

them as well. If the Examiner has any further concerns, Applicant requests a call to the undersigned at (206) 343-7074.

Respectfully submitted,

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